Transfusion of packed red blood cells in patients with ischemic heart disease

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Describe the consequences of anemia in patients with heart disease.
2. List the risks/benefits of transfusion in anemic patients with heart disease.
3. Use this information in a clinical setting.

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Objective: **To review the current literature concerning the utility of and complications associated with transfusion of packed red blood cells (PRBC) in medical and surgical patients with ischemic heart disease.**

Data Sources, Study Selection, and Data Extraction: **The PubMed database of the National Library of Medicine was searched for all studies investigating the use of PRBC in medical and surgical patients with cardiac disease published since 1999. Relevant background literature from before that date was reviewed for inclusion as well.**

Data Synthesis: **An extensive body of literature has accumulated evaluating the safety and efficacy of transfusion as a therapeutic modality in a wide variety of critically ill patients, including patients with cardiac disease. Most, but not all, of these studies have been retrospective in nature, and methodologies have varied from study to study. Some have involved retrospective reviews of patient records, some have been retrospective analyses of detailed databases prospectively collected for other purposes, and some have been prospective randomized or observational studies. Despite the variability in data sources and study design, with a handful of exceptions, the preponderance of data indicates that transfusion of PRBC in the population of patients with ischemic heart disease is of limited clinical utility and may carry the potential for serious adverse consequences.**

Conclusions: **Based on the current literature, there appears to be no indication for routine transfusion in patients with non-ST-elevation acute coronary syndrome, although anemic patients with ST-elevation myocardial infarction may benefit from this intervention. However, the specific indications for transfusion in this population remain ill-defined. (Crit Care Med 2008; 36:1068–1074)**

KEY WORDS: transfusion; anemia; ischemic heart disease; cardiac surgery; outcomes; complications

In recent years the appropriate role of packed red blood cell (PRBC) transfusion has come under intense scrutiny, with an evolving and expanding body of literature indicating that the risks of such therapy may be greater than, and the benefits less than, what has been traditionally believed. In addition to the well-known acute complications of transfusion, such as acute transfusion reactions, infection with blood-borne pathogens, and the now well-recognized entity of transfusion-related lung injury, this therapy is also associated with number of long-term consequences. The majority of these sequelae are immunologic in nature and include alloimmunization, graft vs. host disease, and immunosuppression. Iron overload is generally only associated with unusually large volumes of transfused PRBCs (≥50 units). Prompted in large part by the results of the Transfusion

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The author has not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e318169251f

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Requirements in Critical Care (TRICC) trial as well as a number of subsequent publications, many practitioners have adopted a more restrictive approach to the use of blood products, most notably PRBCs, in a variety of critically ill patients, including those with ischemic heart disease (IHD) (1). In 1992, several years before the publication of the data from the TRICC trial, the American College of Physicians recommended against the use of PRBC transfusion prompted by an arbitrary "transfusion trigger" (2). No general exception was made for cardiac patients in these guidelines, although symptomatic angina was considered an appropriate indication for transfusion. While the use of PRBCs appears to have diminished, recent data evaluating physician practice indicate that there is still a tendency to transfuse patients who have IHD more liberally than many other critically ill patients (3, 4). The goal of this article is to review the current literature concerning the relationship between anemia and IHD and the impact of PRBC transfusion on medical and surgical patients with underlying coronary artery disease.

Anemia and Cardiac Disease

Numerous studies published in recent years provide convincing data that anemic patients with underlying heart disease have worse outcomes as measured by a variety of variables than do cardiac patients with higher hemoglobin levels.

In a 2004 study, Zeidman et al. (5) compared patients with IHD and anemia with patients who had IHD and normal hemoglobin levels. Patients with anemia were found to be significantly more likely to experience congestive heart failure and arrhythmias and had a higher mortality than did patients without anemia.

Anemia has been shown in several studies to be a risk factor for worse outcomes in acute coronary syndromes (ACS). Cavusoglu et al. (6) evaluated the utility of anemia as a predictor of outcome in patients with ACS. Using a hemoglobin value of 13 g/dL (130 g/L) as their cutoff for the definition of anemia, these investigators found anemia to be an independent predictor of death or myocardial infarction (MI) at 24 months. Sabatine and coworkers (7) reviewed data on nearly 40,000 patients enrolled in several clinical ACS trials for the association between anemia and the 30-day incidence of major cardiovascular events. In patients with ST-elevation MI, the likelihood of death was significantly greater if patients were anemic. Mortality was noted to increase with an odds ratio (OR) of 1.21 for every drop in hemoglobin of 10 g/L below 140 g/L. Among patients with non-ST-elevation ACS, cardiovascular death, MI, or recurrent ischemia increased with hemoglobin levels $<$110 g/L. Interestingly, adverse outcomes were also seen in patients with both ST-elevation and non-ST-elevation events when hemoglobin values were above the upper limit of normal. In a study of women undergoing evaluation for chest pain, anemia (defined as a hemoglobin $<$120 g/L) was found to be an independent risk factor for cardiovascular mortality, despite the fact that no differences were identified between the anemic and nonanemic patients in terms of either ejection fraction or degree of coronary artery stenosis (8). The effect of anemia on the outcomes of elderly patients with IHD has also been evaluated. In a study of patients $\geq$75 yrs of age, anemia, after adjustment for comorbidities and other risk factors, was found to be independently associated with higher mortality, with an OR of cardiac death of 1.28 for every decrease in hemoglobin of 10 g/L below 130 g/L (9). Anemic patients with ACS who survive to discharge have been shown to have worse long-term outcomes than nonanemic patients (10). Worsening anemia has been associated with decreased 2-yr survival, with an OR of death 1.57 for patients with mild anemia (hematocrit 33.1% to 39%) and 2.46 for those with moderate to severe anemia (hematocrit $\leq$33%).

Anemia has also been shown to have an adverse impact on outcomes in patients with underlying heart disease undergoing both cardiac and noncardiac interventions. In a retrospective evaluation of patients with a variety of underlying cardiac diagnoses undergoing various surgical procedures, severe anemia was shown to be a risk factor for postoperative morbidity and mortality, with those patients having hemoglobin levels $<$60 g/L experiencing significantly worse outcomes than did patients with hemoglobin values $>$120 g/L (11). In a study of patients undergoing lower extremity vascular bypass surgery, patients with hematocrits $<$28% had a significantly higher incidence of postoperative myocardial ischemia (12). In a study of $>$6,000 patients undergoing percutaneous coronary interventions, anemia was found to be independently associated with both short-term cardiovascular events and decreased 1-yr survival (13). In a similar study of patients undergoing percutaneous coronary interventions for acute MI, anemia was found to be a significant risk factor for in-hospital, 30-day, and 1-yr mortality as well as for disabling stroke (14).

Do Transfused PRBCs Improve Tissue Oxygenation?

Given the evidence supporting the association between anemia and poor outcomes in patients with IHD, it is natural to consider raising the hemoglobin level by transfusion in an attempt to improve outcomes. However, the efficacy of transfused PRBCs appears to be significantly more limited than is often appreciated. Although raising the hemoglobin level will virtually by definition increase the arterial oxygen content and global oxygen delivery, the ability to translate this increase into higher delivery and utilization at the cellular level is more questionable.

Stored PRBCs undergo a variety of morphologic and biochemical changes that adversely affect their ability to fulfill their primary function, the delivery of oxygen to tissue. Biochemical changes include a low P50 and the loss of 2,3,diphosphoglycerate, both of which result in enhanced hemoglobin affinity for oxygen and, consequently, an impaired ability to offload oxygen at the cellular level. In addition, stored PRBCs undergo morphologic deterioration. Within 2 wks of storage, the cells become shrunken, stiff, and deformed, with a resultant decreased ability to traverse the microcirculatory bed. Hemolysis of transfused PRBCs is common and results in the release of free hemoglobin and a variety of other biologically active substances into the circulation, which may trigger an inflammatory response and induce vasoconstriction, exacerbating diminished microvascular perfusion. As the average age of PRBCs transfused in the United States is 17 days, a substantial fraction of all transfused blood has been subject to this degradation before administration (15).

Most studies that have evaluated the ability of transfused PRBCs to increased oxygen delivery at the cellular level have been performed in patients in shock, primarily septic shock, and have been recently reviewed elsewhere, with Napolitano and Corwin (16) focusing on the

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efficacy of transfusion in the critically ill, and Gould and coworkers (17) more broadly reviewing the limitations and clinical consequences associated with PRBC transfusion in a variety of critically ill patient populations. The preponderance of data indicates that while global oxygen delivery is increased following transfusion, the cellular uptake of oxygen, as measured by various variables, including calculated oxygen consumption, lactic acid level, and gastric intramucosal pH, is relatively unaffected by this intervention. Whether certain subgroups of patients can be predicted to respond to PRBCs with increased oxygen consumption is unclear. Conrad et al. (18) were able demonstrate increased oxygen consumption in a subset of septic shock patients with low oxygen extraction ratios before transfusion. Responders had pretransfusion oxygen extraction ratios of <24%. Conversely, in a population of coronary artery bypass patients with low postoperative hematocrits (<25%), Seghal and coworkers (19) concluded that an oxygen extraction ratio of 50% is an appropriate threshold to serve as a transfusion trigger. The typical myocardial oxygen extraction ratio of 50% significantly exceeds the normal global oxygen extraction ratio of 25% to 30%. How this influences the need for and response to transfusion at the cellular level in patients with IHD remains uncertain, however. Suttner et al. (20) compared the effect of transfusion with that of the administration of 100% oxygen on oxygen transport and utilization variables in patients undergoing coronary artery bypass grafting (CABG). Both therapies increased systemic oxygen delivery but failed to change oxygen consumption. The administration of 100% oxygen, but not PRBCs, resulted in an increase in skeletal muscle oxygen tension, attributed by the authors to increased convective oxygen transport resulting from a greater concentration gradient in these patients.

Transfusion and Outcomes in Patients With Ischemic Heart Disease

The ultimate goal of all therapy in IHD is to restore adequate oxygen delivery to the myocardium. As anemia has clearly been identified as a risk factor for poor outcomes with IHD, transfusion, often to some arbitrary threshold, is commonly employed with this purpose in mind. Several large retrospective studies and meta-analyses as well as a limited amount of prospective data directly address the question of whether transfusion is beneficial in this population. Most but not all of the available data indicate that transfusion is generally not useful in these patients and may in fact adversely affect outcomes overall.

As part of a 1997 retrospective assessment of transfusion practices in Canadian intensive care units, the TRICC investigators evaluated the association between transfusion and outcomes in critically ill patients with cardiac disease (21). PRBC transfusion (1–3 units and 4–6 units) was found to be associated with decreased mortality in cardiac patients with hemoglobin values <95 g/L, with an OR for death of 0.80 for each 10-g/L increase in the hemoglobin after transfusion. Subsequently, these investigators performed a prospective trial comparing a restrictive transfusion strategy (transfusing when hemoglobin was <70 g/L, with a target of 70–90 g/L) with a liberal transfusion strategy (transfusing when hemoglobin was <100 g/L, to a target level of 100–120 g/L) in a diverse population of critically ill patients, which demonstrated that the more restrictive transfusion strategy was no worse than the more liberal approach and in some patients was associated with better outcomes (1). In a subsequent article, these investigators reported the results of their analysis of the subgroup of patients with cardiac disease (22). Among all 357 patients with underlying cardiac disease (160 restricted, 197 liberal), baseline characteristics and mortality were similar for patients in both groups, but those in the liberal transfusion group developed significantly more organ dysfunction. A subset of 257 patient with severe IHD (MI or unstable angina) were subsequently analyzed, 111 in the restricted group and 146 in the liberal group. No significant differences in survival were identified for any time period evaluated (30-day, 60-day, intensive care unit, or hospital survival), indicating that there was no benefit to transfusing critically ill patients with IHD if the hemoglobin was >70 g/L, although the authors pointed out that most patients had multiple other active medical problems and that coronary artery disease was not the primary reason for intensive care unit admission for the majority of these patients.

Wu et al. (23) reported on the results of their review of data contained in a Medicare database. They reviewed data on almost 79,000 patients aged ≥65 yrs who had been hospitalized with a diagnosis of acute MI. Patients were classified according to baseline hematocrits and were evaluated for any association between PRBC transfusion and 30-day mortality. These investigators identified an association between the use of PRBCs and improved outcomes in elderly patients when admission hematocrit values were <33%. A greater benefit of transfusion was observed with lower hematocrits; the OR for death was noted to increase in association with transfusion as baseline hematocrit increased. Any benefit of transfusion was lost at a hematocrit >33%, and patients with hematocrits >36% who received PRBCs had an increased risk of death compared with nontransfused patients. The authors concluded that in elderly patients with acute MI and low hematocrits (<33%), PRBC transfusion was beneficial.

In 2004, Rao et al. (24) performed a meta-analysis of data that had been collected as part of the GUSTO IIb, PURSUIT, and PARAGON B trials of patients with ACS. Slightly >24,000 patients were enrolled in these trials, 10% of whom received transfusion of PRBCs. Transfused patients were noted to be older and to have more comorbidities and lower hematocrits than nontransfused patients. When adjusted for these variables, the risk of death, 30-day mortality, and death or MI as a combined end point was significantly higher in the transfused group. Mortality was greater in the transfusion group when the lowest hematocrit was ≥25%; below this value there was no difference in mortality between transfused and nontransfused patients.

Yang and coworkers (25) reviewed data from the CRUSADE National Quality Improvement Initiative to assess the implications of transfusion in patients with non-ST-elevation ACS not undergoing cardiac surgery. Data on >74,000 patients were evaluated in this study. Transfused patients were found to be sicker at baseline, but after adjustment for an extensive list of clinical and demographic characteristics, transfusion remained significantly associated with death and death or MI as a combined end point.

In their study using data from 16 ACS studies, Sabatine and coworkers (7) found differing results among patients with ST-elevation myocardial infarctions (STEMI) and those with non-ST-elevation ACS. Patients with STEMI and hemoglobins <120 g/L had improved outcomes

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when transfused, although those with higher hemoglobin levels did not. Conversely, patients with non-ST-elevation ACS were found to have worse outcomes if transfused regardless of their hemoglobin level.

More recently, Singla et al. (26) reported on outcomes in patients with anemia and suspected ACS receiving transfusion, using data prospectively collected as part of an ongoing registry. Anemia in this study was classified based on hemoglobin level as mild (105–115 g/L), moderate (90–104 g/L), and severe (<90 g/L). After adjustment for other risk factors, transfused patients had a higher risk of either death or recurrent MI at 30 days. The incidence of adverse outcomes was higher in the patients with mild and moderate anemia who had received PRBCs. Transfused patients with severe anemia had slightly better outcomes than nontransfused patients, but this difference did not reach statistical significance.

All of these studies suffer from limitations that may affect the interpretation of their results and make direct comparisons difficult. While the TRICC trial was performed as a randomized, prospective trial, the evaluation of cardiac patients was not its primary goal, and the majority those subjects with IHD had significant concurrent serious illness. The retrospective studies by Wu et al. (23), Rao et al. (24), Yang et al. (25), and Sabatine et al. (7) differ in both patients and methodologies. Wu et al. evaluated only elderly patients, included those with both STEMI and non-ST-elevation ACS, and relied on an administrative database for information. Rao et al. and Yang et al. included patients of all ages, included patients with non-ST-elevation ACS only, and used data which had been prospectively collected for research purposes. Sabatine et al. separately evaluated patients with STEMI and non-ST-elevation ACS. All attempted to adjust for differences within their study populations by using regression analyses, but the variables included in those analyses varied from study to study. Wu et al. adjusted results for a substantially narrower range of possible confounders than did Rao et al., Yang et al., and Sabatine et al. The results reported by Wu et al. and Sabatine et al. suggest that transfusion may be useful in cases of acute MI, although the data presented by Sabatine et al. indicate that its utility be limited to those with STEMI. Wu et al. also limited their evaluation to patients ≥65 yrs of age, a restriction not present in any of the other studies. Whether age is a factor in determining the impact of transfusion in the setting of acute coronary ischemia remains to be determined.

Table 1. Studies on transfusion and outcomes in ischemic heart disease

First Author (Text Reference)	Year	Design	Primary Results
Hebert (21)	1997	Retrospective	Increased survival with transfusion
Hebert (22)	2001	Prospective[a]	No difference in mortality/increased organ dysfunction with transfusion
Wu (23)	2001	Retrospective	Increased survival with transfusion
Rao (24)	2004	Retrospective/ meta-analysis	Increased mortality, combined death/MI
Sabatine (7)	2005	Retrospective	Decreased mortality in STEMI Increased mortality in non-ST-elevation ACS
Yang (25)	2005	Retrospective	Increased mortality, combined death/MI
Singla (26)	2007	Prospective[b]	Increased mortality, recurrent MI

MI, myocardial infarction; STEMI, ST-elevation myocardial infarction; ACS, acute coronary syndrome.
[a]Sub-group analysis of a larger prospective study (1).
[b]Review of data prospectively collected for a registry.

On balance, the existing literature does not support the routine use of PRBC transfusion in patients in cases of non-ST-elevation ACS. There is some suggestion that anemia may be an appropriate indication for transfusion with PRBCs, particularly in the setting STEMI and/or in elderly patients, but this is not conclusively proven by the available data. The appropriate threshold for transfusion also remains undefined, although in the setting of STEMI it may be as high as 120 g/L (7, 23). A summary of the studies evaluating the impact of transfusion on patients with IHD is provided in Table 1. It is notable that the results of all the ACS studies that used prospectively collected data are broadly similar, demonstrating no benefit to transfusion in this condition and, in most cases, an increase risk of adverse effects associated with this therapy.

Transfusion in Cardiac Surgical Patients

Following revascularization of the coronary circulation, with restoration of or at least improvement in myocardial perfusion, the ability to tolerate anemia should be expected to improve.

The safety of a lower hemoglobin threshold for transfusion in postoperative CABG patients was documented in a prospective study performed by Bracey et al (27). These investigators found no difference in outcomes in patients transfused when their hemoglobin dropped below 80 g/L as compared with those transfused at a higher threshold value with the exception of a shorter duration of postoperative mechanical ventilation in the restricted transfusion group. In addition to objective outcome variables, self-reported well-being was similar for patients in both groups.

Numerous studies have appeared in recent years documenting significantly worse outcomes and complications in cardiac surgical patients receiving postoperative transfusions.

In a 1998 prospective observational study, Spiess et al. (28) evaluated the impact of the hematocrit at the time of intensive care unit admission on cardiovascular outcomes in postoperative CABG patients. Hematocrits were categorized as low (≤24%), medium (25% to 33%), and high (>33%). The risk of adverse cardiovascular outcomes (MI and severe left ventricular dysfunction) rose in an incremental fashion as the hematocrit level increased from low to medium to high, with a significant difference detected between the high- and low-hematocrit groups. Among high-risk patients, all-cause mortality was also greatest in the high-hematocrit group. Low output heart failure was shown in a recent study to be independently associated with intraoperative transfusion in patients undergoing CABG surgery (29). While heart failure was also associated with anemia, PRBC transfusion independently increased the risk of this complication.

In 2002, Engoren et al. (30) reported on a retrospective evaluation of the long-term outcomes of >1,900 patients who had undergone CABG over a 42-month period, 34% of whom had received perioperative transfusions. The 5-yr mortality

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was 15% among transfused patients and 7% among those not transfused. After adjustment for comorbidities and other risk factors, the relative risk of death was found to be 1.7 for patients who received transfusions ($p = .001$).

Two recent large studies confirmed the increased risk of mortality associated with transfusion in patients undergoing CABG surgery. Kuduvalli et al. (31) reviewed the records of >3,000 patients and found higher mortality rates among transfused patients at 30 days and 1 yr when compared with nontransfused patients. Koch et al. (32) reported on almost 12,000 patients treated over a 7-yr period. In this evaluation, transfusion was significantly associated with not only mortality but also renal failure, prolonged postoperative ventilatory support, infection, cardiac complications, and neurologic events.

In addition to mortality, a variety of other postoperative complications have been identified in CABG patients receiving PRBC. In addition to Koch et al. (32), other investigators have identified transfusion as an independent risk factor for postoperative infection (33–35), although others were not able to demonstrate any increased rate of infection associated with transfusion in this population (36). Prolonged mechanical ventilation has been associated with the volume of red blood cell supernatant in CABG patients but not with other fluids administered (platelet supernatant, plasma components, total transfused fluid) (37). A significant increase in the risk of new-onset atrial fibrillation in cardiac surgical patients was recently independently associated with transfusion as well (38). Intraoperative transfusion with PRBCs has been identified as an independent risk factor for renal injury (both percentage change in creatinine and development of acute renal failure) in patients undergoing cardiopulmonary bypass during CABG surgery (39).

In addition to the acute adverse effects of PRBC transfusion in this population, data suggest that long-term sequelae occur as well. In a follow-up study of >12,000 patients, Koch et al. (40) used the Duke Activity Status Index as an indicator of self-assessed quality of life, comparing preoperative with 6- and/or 12-month postoperative scores. After adjustment for other factors, these investigators found that quality of life was incrementally worse with more PRBCs administered. Platelet administration was also found to be associated with worse scores. Table 2 summarizes the studies reviewing the impact of transfusion in cardiac surgical patients.

Table 2. Studies on transfusion and outcomes in cardiac surgery patients

First Author (Text Reference)	Year	Design	Primary Results
Spiess (28)	1998	Retrospective	Increased MI, LV dysfunction with transfusion
Bracey (27)	1999	Prospective	No difference in outcomes Shorter duration of postoperative mechanical ventilation in restricted transfusion group
Leal-Noval (33)	2001	Retrospective	Increased postoperative infection
Engoren (31)	2002	Retrospective	Increased 5-year mortality
Vamvakas (37)	2002	Retrospective	Increased postoperative ventilator time
Ali (34)	2004	Retrospective	No association with infection
Kuduvalli (30)	2005	Retrospective	Increased mortality with transfusion
Sreeram (35)	2005	Retrospective	Increased postoperative infection
Habib (39)	2005	Retrospective	Increased renal injury
Banbury (36)	2006	Retrospective	Increased postoperative infection
Koch (32)	2006	Retrospective	Increased mortality, renal failure, infection, ventilator time, cardiac complications, neurologic events with transfusion
Koch (38)	2006	Retrospective	Increased risk of atrial fibrillation with transfusion
Koch (40)	2006	Prospective[a]	Lower scores on quality of life assessment at 6 and 12 months with transfusion
Surgenor (29)	2006	Retrospective	More low output heart failure with transfusion

MI, myocardial infarction; LV, left ventricular.
[a]Quality of life data collected prospectively.

The American Society of Anesthesiologists offered a series of guidelines on the use of perioperative transfusion in 2006, although these were general in nature and not directed at the cardiac surgical patient population in particular (41). Transfusion was recommended at a hemoglobin level <60 g/L, and it was specifically noted that transfusion is rarely necessary at hemoglobins >100 g/L. For intermediate hemoglobin values it was recommended that the decision to transfuse be based on the assessment of a variety of clinical variables, including evidence of organ ischemia, potential or actual ongoing bleeding, the patient's intravascular volume status, and the patient's risk factors for complications of inadequate oxygenation. In 2007 the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists issued an extensive report and set of clinical guidelines on perioperative transfusion and blood conservation strategies in cardiac surgical patients (42). Postoperative transfusion with PRBCs was specifically recommended in these guidelines for patients with hemoglobins <60 g/L and was felt to be a reasonable intervention in those with hemoglobin levels <70 g/L, although the authors noted that there was no high-level evidence to support this recommendation. No recommendations were made for routine transfusion at higher hemoglobin levels.

As in medical cardiac patients, the availability of prospective data evaluating the impact of transfusion on cardiac surgical patients is quite limited. The available data indicate that overall, transfusion in this population is associated with significantly worse outcomes as measured by a variety of variables: mortality, infection, postoperative duration of mechanical ventilation, and postoperative atrial fibrillation, among others. Although predominantly retrospective in nature, the consistency of these findings supports the position that transfusion should be used extremely judiciously in cardiac surgical patients.

Are There Alternative Treatments for Anemia?

Unfortunately no existing anemia treatments other than transfusion are capable of rapidly raising hemoglobin and thus they are ineffective as adjuncts in the management of acute ischemia in anemic patients. This leaves open the question of whether pharmacologic therapy for anemia is beneficial in patients with IHD.

Iron supplementation has historically been the mainstay of treatment for many patients with chronic anemia. Concern

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about the possible role of increased iron stores as a risk factor for coronary artery disease has been debated for years. Recent evaluations of the available literature suggest that no significant association between iron and the risk of IHD disease exists (43). However, outside of the renal population, there are few data on the impact of chronic iron supplementation on outcomes in anemic patients with IHD.

Stimulation of erythropoiesis by the use of agents like erythropoietin and darbepoetin has been used extensively in patients with renal failure and other causes of chronic anemia (such as cancer) for many years. Data on the utility of these agents in patients with IHD are scarce. A recent randomized trial enrolling 22 patients with acute MI evaluated the effect of a single dose of darbepoetin (44). No significant change in hematocrit was found, despite an increase in erythropoietin levels in recipients to levels as high as 270 times the level of controls. While no adverse effects were identified in recipients of darbepoetin, at 4 months there was no significant difference in ejection fraction between the groups detected. Erythropoietin may have beneficial effects in patients with IHD separate from any augmentation of hematocrit. Evidence for a tissue-protective effect of this agent has recently been reviewed and suggests a possible future role for erythropoietin in the chronic management of patients with IHD (45, 46). It remains uncertain whether an acute role exists for this agent in the management of IHD.

Among surgical patients, minimization of blood loss is a key aspect in the prevention and management of anemia. The guidelines offered by the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists provide an extensive review of adjunctive interventions to reduce the risk of perioperative bleeding and decrease the potential need for transfusion in cardiac surgical patients (42). Class I recommendations are made for the use of antifibrinolytic agents, such as aprotinin (a protease inhibitor) and ϵ-aminocaproic acid or tranexamic acid (lysine analogues). Concerns regarding the safety of aprotinin were raised by an observational study published in 2006 which indicated that this agent was associated with an increased risk of serious cardiac, renal, and neurologic complications, including MI, renal failure, and stroke (47). In November 2007, the manufacturer of aprotinin agreed to stop marketing this agent in the United States and in other countries at the request of various governmental agencies. Preliminary results of a Canadian study, the "Blood conservation using antifibrinolytics: A randomized trial in a cardiac surgery population" (BART study), indicated higher mortality among those treated with this drug, prompting cessation of the trial and withdrawal of the drug from the market. The use of red cell-saving devices also receives a class I recommendation. Other pharmacologic interventions, including the use of erythropoietin, desmopressin acetate (DDAVP), and protamine receive class II recommendations and are limited to specific patient populations.

CONCLUSION

Much attention is paid today to the concept of evidence-based medicine. However, when the evidence contradicts established practice or long-held beliefs, modification of one's practice may be difficult. Although the detrimental effect of anemia on outcomes in patients with ischemic heart disease is well established, it does not follow that correction of the anemia by transfusion is inherently beneficial. An extensive body of literature has accumulated, time and again documenting significant complications associated with and limitations in the efficacy of transfusion of PRBCs. While much of this literature is based on retrospective data analyses, with few exceptions the findings have been remarkably consistent from study to study. The limited prospective data that are available are in concordance with the general findings that transfusion of PRBCs carries limited utility and significant risk in a broad array of patient populations, including patients with heart disease. While circumstances likely exist in specific patients and populations where transfusion is appropriate, the current data strongly suggest that these situations are significantly less common than routinely believed. Ideally, a large prospective study specifically designed to evaluate the impact of transfusion in this population would resolve this question definitively. In the absence of such a study, however, based on the available literature, limitation of transfusion to a relatively small portion of the medical and surgical cardiac patient population seems indicated.

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